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SUMMARY

The present thesis examined the genetic architecture of attention problems, attention, executive functioning, and intelligence (IQ). In addition, the (longitudinal) genetic relations among attention problems, executive functioning and IQ were investigated. Data were collected twice in a sample of twin children registered at the Netherlands Twin Registry (NTR): when they were 5 years old, and seven years later, when they were 12 years old. In this last chapter the results as presented in this thesis and other publications that have resulted from this project will be summarized and discussed.
First the genetic architecture of attention problems as assessed by different instruments and by different raters at ages 5 and 12 years is summarized. Next, an overview of the genetic studies on executive functioning and IQ, and their relation to attention problems is presented. Finally, the results of this thesis are discussed and put into the perspective of future directions for research into attention and attention problems.

Attention Problems

Attention problems in 5 and 12-year-old children were assessed by asking parents, teachers and children themselves to rate their behaviors. Genetic analyses of teacher ratings in young children are scarce. Chapter 3 presents a study on the sources of variation in the Teacher's Report Form (TRF, Achenbach, 1991a) problem scales in 5-year-old children. In the genetic modeling we accounted for differences in ratings between twin pairs rated by the same teacher and twin pairs rated by different teachers. Means and variances of all problem scales, including the attention problem (AP) scale, were lower and twin correlations were higher, for children who were rated by the same teacher, compared to children who were rated by different teachers. The heritability estimates of the eight problem scales of the TRF (Anxiety, Social problems, Withdrawn, Aggression, Rule breaking, Somatic complaints, Thought problems, and Attention problems) ranged between 30 and 63%.
Chapter 2 presents longitudinal genetic analyses (age 5 and 12) on the AP scale as rated by parents and teachers. Parental ratings on attention problems at age 5

Table 1
Monozygotic (MZ) and dizygotic (DZ) twin correlations for attention problems as assessed with behavior questionnaires at age 5 and at age 12 in the current sample and in larger samples of the NTR.

Age 5	N twin pairs	MZ	DZ
DCB M[1]	228	0.60	0.04
DCB M Van Beijsterveldt et al. (2004)	7679	0.62	0.05
ASH M	234	0.77	0.15
TRF T[1]	209	0.80	0.48
ASH T	209	0.73	0.33
Conners (old version) T	209	0.72	0.39
Age 12			
CBCL M	198	0.68	0.08
CBCL M Rietveld et al. (2004)	1516	0.72	0.26
CBCL M Derks et al. (in revision)	2850	0.75	0.34
Conners M	181	0.79	0.10
Conners M Derks et al. (in revision)	2443	0.84	0.38
SWAN/Hyperactivity M	561[2]	0.91	0.43
SWAN/Attention Deficit M	561[2]	0.85	0.38
TRF T	94	0.72	0.25
Conners T	90	0.63	0.24
YSR C[1]	172	0.51	0.33

Note [1]: M = mothers, T = teachers, C = children
Note [2]: original sample extended with SWAN data of additional 12-year old NTR sample

were collected with a short form of the Devereux Child Behavior Rating Scale (DCB, Spivack & Spotts, 1966; Van Beijsterveldt et al. 2004). At age 12 parental ratings were of AP were obtained with the Child Behavior Checklist (CBCL, Achenbach, 1991b). For teacher and parental ratings longitudinal genetic analyses on the AP scales were performed. For teacher ratings the pattern of twin correlations indicated influences of additive genetic factors at age 5 and at age 12. For parental ratings at both ages DZ correlations were lower than half the MZ correlations, pointing to additive and non-additive genetic factors influencing variation in AP. The heritability estimates for attention problems at age 5 and 12 as rated by their parents were 59% and 67%, and as rated by the teachers 81% and 71% respectively.

Other behavior questionnaires assessing attention problems that were collected at age 5 were the Conner's Rating Scale (Conners, 2001) as rated by teachers, and the Aandachttekort Stoornis met Hyperactiviteit (ASH, Gunning, 1992) as rated by parents and teachers. At age 12 the Youth Self Report (YSR, Achenbach, 1991c) was collected. There are no publications of the current sample on these instruments but Table 1 provides an overview of twin correlations of AP measures on all behavior questionnaires assessed at age 5 and 12 in the current sample. When available, twin correlations for these questionnaire data that were published in larger NTR samples are also included.

At age 12 data on the Strengths and Weakness of ADHD symptoms and Normal behavior Scale (SWAN, Swanson et al. 2006) were collected. These data were also available in an additional NTR sample that was selected for attention problems (Derks et al. 2006a). The SWAN measures Hyperactivity/Impulsivity (HI) and Attention Deficit (AD) with item scores on a 7 point scale, ranging from 'average behavior' to the extremes 'far below average' and 'far above average'. So in contrast to most regular checklists the SWAN scores cover the strengths as well as the weaknesses of a child, ranging from severe hyperactivity to normal activity and from serious attention deficits to a high level of attention. The results of this study, presented in chapter 4, showed that scores on the SWAN rating scales show a normal distribution. Variation on the SWAN/HI and SWAN/AD scale was explained by additive genetic influences (90% and 82% respectively) and unique environmental influences.

Attention (Problems) and the snap-25 Gene

An association study was performed between Single Nucleotide Polymorphisms (snp's) on the snap-25 gene and swan/hi and swan/ad scores. Previous studies have reported significant associations between the snap-25 gene and attention problems (Barr et al. 2000; Brophy et al. 2002; Mill et al. 2002; Kustanovich et al. 2003; Feng et al. 2005; Mill et al. 2004). The snap-25 gene is differentially expressed throughout the brain and is during development involved in synaptic plasticity, dendrite formation and axonal growth. In addition the gene has a regulatory role in the dopamine system (Osen-Sand et al. 1993; Grosse et al. 1999). The results presented in chapter 5 showed that of 8 tagging snp's, covering the snap-25 gene, one snp was significantly associated, and two snp's showed a trend for association, with scores on the swan/ad scale. The significant snp has also been found to be associated with iq in this sample (Gosso et al. 2006).

Executive Functions

The genetic background of three different aspects of executive functioning was investigated, namely of working memory, selective- and sustained attention. Working memory and attention are mainly anchored in the frontal brain regions (Fuster, 1997; Smith & Jonides, 1999; Carpenter et al. 2000; Hampson et al. 2006), and these areas are partially overlapping with neural systems that seem to be affected in neuropsychiatric disorders like adhd (Castellanos & Tannock, 2002; Casey & Durston, 2006; Durston et al. 2006). Previous studies had reported impairment of these functions in children with attention problems (Swaab-Barneveld et al. 2000, Swanson 2003; Joseph 1999, Pennington & Ozonoff, 1996; Tannock, 1998; Barkley, 1997; Manly et al. 2001). A sub sample of the current sample was compared with children diagnosed with adhd on inhibition tasks (Slaats-Willemse et al. 2003) and selective- and sustained attention tasks (Stins et al. 2005). The affected adhd group performed significantly worse on reaction time and accuracy than the normal twin controls.

In chapter 6 the genetic background of working memory was analysed. A distinction was made between working memory speed and capacity and the phenotypic and genotypic relationship between these working memory components was investigated. The phenotypic correlation between working memory speed and

Table 2:
Overview of twin correlations of IQ, working memory, selective attention, and sustained attention at age 5 and at age 12, and the Stroop, Flanker and Simon tasks at age 12

Age 5	N twin pairs	MZ	DZ
IQ	237	0.68	0.54
Working Memory	235	0.55	0.35
Selective attention	233	0.50	0.35
Sustained attention	237	0.60	0.28
Age 12			
IQ	176	0.81	0.43
Working Memory	171	0.73	0.54
Selective attention	171	0.60	0.48
Sustained attention	172	0.61	0.49
Stroop RT	170	0.80	0.39
Stroop effect	170	0.52	0.15
Flanker RT	157	0.43	0.38
Flanker effect	157	0.18	0.26
Simon RT	156	0.51	0.28
Simon effect	156	0.19	0.10

capacity was -0.30, demonstrating that both components involve partly similar working memory processes. The genetic correlation was -0.54 which indicates that working memory speed and capacity are partly mediated by the same set of genes. As on a phenotypic level intelligence and working memory performance

are strongly related (Kyllonen and Christal 1990, Colom et al. 2004) it was tested whether the genetic correlation of -0.54 was not explained by intelligence (*g*), instead of a genetic relation between working memory speed and capacity per se. Adding general IQ to the genetic models revealed that both *g* and working memory itself are responsible for the shared genes between working memory speed and capacity.

In chapter 7 working memory, selective- and sustained attention were analysed in a longitudinal genetic design. These results showed that in young children (age 5) the relative contribution of genes on variation in these executive functions ranged between 28 and 59%, and in older children (age 12) between 42 and 73%. It was also shown that the stability over time of working memory, selective- and sustained attention was due to genetic factors only. At age 12, the genetic influences on variation in executive functioning could be distinguished into stable genetic effects, which were transmitted over time, and new genetic influences which emerged at age 12. The longitudinal genetic correlations of executive functioning were between 26 and 59%. Table 2 presents an overview of twin correlations of IQ and the executive functions as investigated in this thesis.

Attention Problems, Executive Functions and Intelligence

Chapter 2 of this thesis describes genetic influences on variation in IQ during childhood. In young children (age 5) common environmental and genetic factors play an equally important role explaining 37% and 31% of the total variance respectively. At age 12 years the influence of common environment has disappeared and the heritability is estimated as 81%. Also the longitudinal genetic relation between these traits was investigated. The longitudinal phenotypic correlation between IQ at age 5 and IQ at age 12 was 0.51, and the longitudinal genetic correlation was 0.81.

It was examined to what extent IQ performance, executive functions, and attention problems at age 5 predicted IQ performance at age 12. Executive functioning at age 5 was only weakly correlated with IQ scores at age 12 (r = 0.10 - 0.16). The genetic correlations fell in the same range except for selective attention of which the longitudinal genetic correlation with IQ was higher, namely 0.31. Thus, the phenotypic correlation is partly explained by common genes.

Notable was the significant phenotypic correlation between attention problems at age 5, as rated by mothers and teachers, and IQ performance at age 12 (r = -0.28 and -0.36 respectively). This means that attention problems in preschool children are predictors for IQ scores later in childhood. The longitudinal phenotypic correlation was partly explained by a common genetic factor; the genetic correlations were -0.42 and -0.39 respectively. In other words, there is a common set of genes that influences attention problems at age 5 and IQ performance at age 12.
At age 5, executive functions among each other showed very high genetic correlations (r = 0.80, 0.82 and 0.90), and with IQ the genetic correlations were between 0.36 and 0.70. The genetic correlation between executive functioning and attention problems as rated by the teacher ranged between -0.31 and -0.38 (both at age 5). The genetic correlation between executive functioning and maternal ratings of attention problems at this age was low (-0.17 - 0.08).

DISCUSSION

In this final part the findings of this thesis and related publications are interpreted and future directions will be discussed.

Attention Problems Assessed by Behavior Checklists

When multiple raters are used to rate a child's attention problems the situational variation in children's behavior can be taken into account. For example, teachers can report on problems that are specific to the classroom or other school situations, such as problems in the social interactions with other children, or task oriented situations, while parents have unique information about the child's behavior in the family environment. In a similar vein will children themselves have a unique view on their own behavior, at school, at home, with friends or at the sports club (Verhulst et al. 1997; Van der Ende & Verhulst, 2005).
There is only a moderate correlation between parental and teacher assessments of attention problems (Achenbach & Rescorla, 2000; Van der Ende & Verhulst, 2005), while correlations between ratings of parents are generally higher (Derks et al. 2006a). Notable in chapter 3 of this thesis was the fact that also between

teachers there might be differences in their ratings, which may originate from 'specific teacher styles'. These teacher styles can cover a whole range of domains, including personal values and pedagogic qualities but also school systems, social interaction with the children, and educational approaches. Some teachers for example prefer strict rules in the classroom whereas others have a more lenient style. Some children prosper better under free conditions whereas others need a structured environment. One approach to look at this is by obtaining ratings of the twins from multiple teachers. This could be done by asking teachers of specific disciplines, like music or gymnastics, to complete a behavior checklist, or by a regular assessment of the TRF, as children (in the Netherlands) change teachers almost every school year. The longitudinal data collection of the TRF by the NTR may provide the latter opportunity within a few years.

The heritability estimates of attention problems as derived from different raters and different checklists are rather similar and range between 60 and 90%. The SWAN, described in chapter 4, is a questionnaire measuring the continuum of attention. It showed heritability estimates that were slightly higher as those of regular checklists that measure attention problems only. Remarkable was that no influences of dominance (non-additive genetic effects) were detected which is in contrast to previous studies on attention problems. Especially with parental ratings heritability estimates consist often of additive and non-additive genetic effects. One can speculate whether earlier found dominance effects are real or whether they may be an artifact of the format of regular, narrow ranged checklists (i.e., parents have the possibility to rate their child's behavior with ' never', 'sometimes', or ' often'). The pattern of very low DZ correlations that are usually found with parental checklists may therefore point to contrast effects instead of dominance effects. Contrast effects may arise because parents compare the behavior of their twins and stress differences between them (Eaves et al. 1997; Simonoff et al. 1998), and regular checklists may enhance these contrast effects. This is to a lesser extent the case with the SWAN rating scale; instead of the 'all' or 'not' possibility as on regular checklists, parents have on the SWAN scale the opportunity to rate their twins differentially on a much broader range. Due to this broader range, covering the continuum of attention, SWAN scores of both the Hyperactivity and Attention Deficit scale were normally distributed. This

supports the idea that attention problems are not a dichotomous trait (i.e., 'you have attention problems or not'), but indicates that attention and attention problems are normally distributed in the population, with children that have severe problems positioned on the extreme tail of the distribution.

The Search for Genetic Polymorphisms

When a large heritability is found, as was the case for attention and attention problems, it should be possible to localize and identify genes that explain this heritability. Whether or not such undertaking will lead to positive results with the current phenotypes and the current genetic and genomic approaches is still a matter of discussion, as indicated below.

We carried out an association study between the SWAN scores and polymorphisms in the SNAP-25 gene. Two SNP's on this gene showed a trend for association, and one SNP was significantly associated with scores on the AD scale of the SWAN. The latter SNP showed also a significant association with IQ in this sample. In other words, we found evidence for a possible mediating role of the SNAP-25 gene for attention and attention problems, and for IQ. In the last decade several other association studies as well as linkage projects have been conducted to find genes that are related to attention problems and ADHD. The foci of these studies have been mainly on mechanisms underlying the dopaminergic neurotransmission systems. Brain imaging studies of affected children suggested that brain regions with rich dopamine content were involved in ADHD (Tannock et al. 1998). The significant reduction of ADHD symptoms after using pharmacological medication (for example methylphenidate) that primarily act on the dopaminergic system additionally pointed to a significant role of the dopamine system in ADHD pathology (Spencer et al. 1996).

With candidate gene studies several genes in the DA and related path ways have shown a statistically significant association with ADHD in three or more studies. These are Dopamine Receptor D4 (DRD4), Dopamine Receptor D5 (DRD5), Dopamine Transporter (DAT), Dopamine α-Hydroxylase (DBH), Serotonin Transporter (5-HTT), Serotonin receptor (HTRIB), and synaptosomal-associated protein 25 (SNAP-25) (Faraone et al. 2005). However, conflicting results are also reported. For example Hebebrand et al. (2006) could not replicate significant

association for the DAT1 VNTR gene, which is located under the linkage peak they found. Also a meta-analysis by Purper-Ouakil et al. (2005) found no evidence for association of the DAT gene. Of the four genome wide linkage studies that have been conducted so far (Fisher et al. 2002, extended by Smalley et al. 2002, Bakker et al. 2003, Arcos-Burgos et al. 2004, Hebebrand et al. 2006) the overlap in results concerned only chromosome 5p; this region showed nominal evidence of linkage in the first three studies, and strong evidence for linkage in the study by Helebrand et al. (2006). Unfortunately none of the putative candidate genes so far are located under chromosome 5p.

Endophenotypes for Attention Problems

In the past years a lot of effort has been put in the identification of endophenotypes that may elucidate the genetic path ways of disorders like ADHD, and ultimately unravel the causing biological mechanism. The role of endophenotypes is to serve as intermediates between the genes and the manifest disorder itself, as the identification of genes influencing the endophenotype might reveal the (related) genes influencing the phenotype of interest at the same time (Gottesman, 1997; Skuse, 2001; Gottesman & Gould, 2003).

Over time evidence has accumulated that symptoms of ADHD are related to impairment in the frontal cortex and subcortical cortices that project to it (Castellanos & Tannock 2002; Casey & Durston 2006, Shaw et al. 2006b). As the prefrontal cortex is one of the crucial brain regions for executive functioning (Fuster, 1997, Smith & Jonides, 1999, Prabhakaran et al. 2000, Carpenter et al. 2000, Hampson et al. 2006) these functions have been proposed as promising endophenotypes. Executive functions cover interrelated but rather distinct cognitive functions like inhibition, sustained attention, selective attention and working memory. A crucial feature of a useful endophenotype is, logically, that variation on this trait is influenced by genes and that the association of the endophenotype and the clinical disorder is mediated by correlated genetic, rather than correlated environmental influenes.

Working memory, selective- and sustained attention are heritable traits during childhood, and their longitudinal stability is explained by genetic factors. In addition strong genetic correlations ($r > 0.80$) among the executive functions were

found. Two previous studies with the current sample investigated the heritabilities of executive functions in children. Groot et al. (2004) reported a heritability of 54% for reaction time measures of inhibition assessed with a computerised Go-No go task at age 5. In the same sample, at age 12, inhibition was measured with the Stroop Color Word task and the Eriksen Flanker task. Heritability estimates for reaction time on card 1, card 2 and card 3 of the Stroop task were 75%, 70% and 74% respectively, and for the Stroop effect (i.e., the difference in reaction time between card 2 and card 3, which is an index of inhibition) the heritability was estimated as 49%. For performance on the Eriksen Flanker task no genetic influences were found (Stins et al. 2004).
Thus, most endophenotypes that have been proposed as endophenotypes show heritability. They are also reliable as was shown in chapter 7 for the endophenotypes assessed at age 12.

Are Endophenotypes Useful for ADHD?

The use of endophenotypes in the search for genes that influence attention problems and ADHD has been subject of discussion recently. First, despite previous results, some doubts about the phenotypic relation between attention problems and proposed endophenotypes have been postulated. "Deficient attention is hard to find" reported Huang Pollock et al. (2005) when investigating selective attention in a sample of children affected with several forms of ADHD. In a meta-analysis Van Mourik et al. (2005) could not find specific impairments in children with ADHD on Stroop Color Word performance. Other studies also suggested that the evidence for impaired cognitive functioning is not unambiguous (Mason et al. 2003; Jonsdottir et al. 2006; Castellanos et al. 2006). As mentioned before, an important criterion for endophenotypes is a meaningful phenotypic correlation with the trait of interest.
Most important problem in identifying specific (cognitive) impairments in children with attention problems involves the neurocognitive heterogeneity among children with ADHD. Not only variability between ADHD subjects, but also variability within ADHD subjects has been reported. Thus, not every person with ADHD is impaired on every test, and some children with ADHD perform on these tests within the normal range while others perform worse (Pennington &

Ozonoff 1996, Doyle et al. 2000, Pasini et al. 2007). Doyle et al. (2005) summarized the problems in identifying useful endophenotypes on a phenotypic level with the following comments. First they consider the complexity, and probably uselessness of the endophenotypes that have been investigated so far. What is lacking specifically is a) precision of the measures of executive function, b) reliability, sensitivity and validity of these measures and c) results based on large sample sizes. Their second worry involved the neurocognitive heterogeneity of ADHD, and especially the fact that up till now not a single core deficit for ADHD has been acknowledged.

Power Problems

A serious concern about the value of intermediate traits on a genotypic level was raised by Plomin et al. (2006). They argued that complex traits and disorders like ADHD are caused by multiple genes of varying but small effects sizes and that genetic effects of underlying traits (like endophenotypes) perhaps explain less than 1% of the variance. To detect significant associations with 80% power for SNP's that have an effect size of 1% very large sample sizes (> 1000 cases and >500 controls) are needed. Plomin et al. (2006) however assumed that an effect size of 1% is yet too optimistic and that an effect size of 0.1% is maybe more realistic. Hence, to obtain enough power for these kinds of effects even much larger samples are needed and the question is whether this is feasible.

Flint and Munafo (2006) performed a meta-analysis on genetic association studies of endophenotypes to examine whether these intermediate traits exhibit larger genetic effects than the manifest disorders specifically, and to discuss the usefulness of endophenotypes in genetic research in general. They showed that the genetic effect sizes of endophenotypes fall in the same range as those for the behavioral phenotypes of interest. Flint and Munafo (2006) therefore openly doubt about the usefulness of endophenotypes in addition to clinical phenotypes. However, they also argue that especially endophenotypes (that are reliable, robust and quantitative measures) may be suitable to collect the large data sets that are needed for the genetic analyses of complex traits.

Attention Problems and Intelligence

In this study a common set of genes was found for attention problems at age 5 and IQ performance at age 12. Kuntsi et al. (2004) reported similar results in a cross sectional design: they found a set of common genes for attention problems and IQ scores, both measured at age 5. They speculated that the common genes that are shared between attention problems and IQ performance may involve brain volume abnormalities that influence both traits. Castellanos et al. (2002) reported persistent brain abnormalities in children with ADHD while Shaw et al. (2006a) reported an association between intelligence and the trajectory of cortical development, primarily in frontal regions. In an accompanying study Shaw et al. (2006b) showed that children with ADHD have relative cortical thinning in regions important for attentional control (i.e., medial and superior prefrontal and precentral regions). An association between brain volume and intelligence was reported by Posthuma et al. (2002) who showed that IQ and brain volume are influenced by shared genetic factors.

In a recent paper by Kovas and Plomin (2006) they proposed the existence of so called 'generalist genes'. This hypothesis is based on the fact that there is a broad genetic overlap in cognitive functions like language, and general intelligence. Kovas and Plomin (2006) therefore assume that the effects of generalist genes are widespread to the brain and not specifically localized. Consequently, these genes affect multiple brain structures and functions, each of which affects multiple cognitive processes (see also Butcher et al. 2006). In chapter 2 of this thesis it is confirmed that cognitive functions like IQ, working memory, selective- and sustained attention, and cognitive dysfunction, like attention problems, have a genetic correlation. At age 5, executive functions among each other showed genetic correlations of 0.80, 0.82 and 0.90, and with IQ the genetic correlations were between 0.36 and 0.70. Also between IQ and attention problems as rated by mothers and teachers substantial genetic correlations were found, not only at age 5, but also longitudinal.

A few studies investigated genetic polymorphisms of the dopamine system that possibly could explain a part of the correlation between ADHD and intelligence. Mill et al. (2006) tested whether the DRD4 seven-repeat allele and the DAT1 ten-repeat allele were associated with variation in intelligence among children with

ADHD. They found evidence for this association in two independent cohorts, from New Zealand and Britain. An attempt to replicate these findings in three larger, independent Brazilian samples by Genro et al. (2006) failed. However, given the 'generalist genes' hypothesis, and the important role for the dopaminergic regulation in attention problems and cognitive functioning (Nieoullon, 2002), a further investigation of the moderating role of dopaminergic polymorphisms seems interesting and relevant for future research.
In the current sample a significant association was found between IQ and the SNAP-25 gene (Gosso et al. 2006). Moreover, the SNP that was found to associate with IQ did overlap with the SNP that was associated with attention problems. For the moment it remains the question whether the SNAP-25 gene serves as intermediate between attention problems and IQ, as was tested for the DAT1 and DRD4 gene by Mill et al. (2006) and Genro et al. (2006). Future research may enlighten the possible moderating role of SNAP-25 in cognitive and attentional processes.

Conclusions

Attention is normally distributed in the population with superb skills and serious problems on the tails of the distribution. In the general population 4 to 12% of the children have severe problems (Brown et al. 2001; Faraone, 2003), often clinically diagnosed as having Attention Deficit Hyperactivity Disorder (ADHD). Variation in attention, attention problems and ADHD is, independently from informants and questionnaires, sex and age, strongly influenced by genetic factors (Derks et al. 2006b). The results of molecular genetic studies however have not been conclusive yet. Problems for identifying genes include the heterogeneity of the behavioural and neurocognitive phenotype of ADHD, and the fact that many genes with each a small effect mediate the symptoms of hyperactivity, impulsivity and attention deficit (Buitelaar 2005; Doyle 2005; Khan & Faraone 2006).
As a promising approach to unravel the genetic path ways of cognitive disorders like ADHD a decade ago the use of endophenotypes was introduced. It is clear however that the endophenotypic approach has not revealed a short-cut to identifying the genetic factors of ADHD so far and the conclusion after all is that the future role of cognitive endophenotypes is uncertain. The phenotypic relation

with the disorder of interest, in this case ADHD, is unclear (Doyle et al. 2005), endophenotypes do not offer a closer link to the genes than clinical phenotypes do (Flint & Munafo, 2006), and the effect sizes of genes influencing the endophenotypes may even be smaller than those of clinical phenotypes (Plomin et al. 2006). On the other hand, endophenotypic data can be collected relatively easy in large samples, on a reliable and valid way. The use of cognitive endophenotypes may also help to define cognitive homogeneous clusters of ADHD patients (Kuntsi et al. 2006). And, as being cognitive traits, endophenotypes are supposed to be influenced by so called generalist genes, which are wide spread to the brain (Kovas & Plomin, 2006). Hence, multivariate molecular genetic analyses on cognitive functions might provide a window through which we can view brain mechanisms that are functionally related to cognitive (dys) functions.

In this thesis substantial heritability estimates were presented for working memory speed and capacity, and for selective- and sustained attention. It was shown that stability of these traits during childhood is due to genetic factors, and in addition substantial genetic correlations between these cognitive functions were found. Notable also were at age 5 the genetic correlations between the executive functions and IQ, and between executive functions and teacher reported attention problems. Hence, despite the (sometimes) low correlations between attention problems and executive functioning on a phenotypic level, the focus of future research should perhaps be on the genetic correlations among cognitive traits and complex disorders. The executive functioning traits as presented in this thesis can have potential value in identifying genes involved in cognitive disorders as across childhood we found (shared) genes that influence these traits and related cognitive (dys) functions. Multivariate analyses in large samples may identify the actual genes that play a mediating role between cognitive functioning and cognitive disorders. As the NTR has over the years collected large data sets on attention problems and cognitive functioning, and as also the data collection of DNA is growing, these studies may be carried out in the nearby future.

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